

**DETAILED ACTION**

Claims 1-16 are pending.

The elected group is Group I claims 1-13 drawn to compounds and pharmaceutical compositions of formula I, where ring A is a 5-6- membered, and ring B at position 6 has a aliphatic hydrocarbon, (the compounds thus have a triazaspiro, undecane, decane or a nonane core.)

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein,

- a) ring A is 6 membered and R and the aliphatic group at R6 are an alkyl substituted by a phenyl or a cyclohexyl, does not reasonably provide enablement for any and all the hydrocarbons.
- b) formula I is of a limited scope of compounds does not enable the "prodrugs", "solvate"
- c) having some antagonist activity of CCR5 does not enable the pharmaceutical composition for preventive/treating activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

**1) The breadth of the claims:** The instant claims encompass many compounds with a different core and different groups hanging off of it.

**2) The nature of the invention:** The invention is a chemical compound used as a pharmaceutical.

**3) The state of the prior art:** The state of the prior art is that the drugs and the enzymes react in a lock and key mechanism and the structure of the compound has to be specific. Even a difference of a methyl group verses a hydrogen changes the properties altogether. A good example is a theophylline verses caffeine. They differ by just a methyl group but one of them has a pharmaceutical use as a bronchodilator. This is just a general example. Applicants claims are drawn to compounds which would be useful in treating HIV. The treatment for HIV is still an unknown and evolving art. Thus at the time of filing very little is known of treating and preventing HIV. There is no absolute predictability and no established correlation between the different substitutions on a core that they would all behave in the exact same way. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Preventive a disease requires some population data to show that the diseases can in fact be 'prevented.' How would one know it was prevented, one does not have any population data.

**4) The level of one of ordinary skill:** The ordinary artisan is highly skilled.

**5) The level of predictability in the art:**

How to use:- It is noted that the pharmaceutical art is unpredictable , requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. The level of unpredictability is in the art is very high. The compounds which differ by a methyl group also show different properties, for c.g. theophylline and caffeine. One of them is a bronchodilator and they differ only by a methyl group. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies

inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

How to make :-

As stated in the preface to a recent treatise:

"Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)

....." Dorwald F. A.

Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

Thus it is not very easy to synthesis compounds.

**6) The amount of direction provided by the inventor:** The inventor provides very little direction in the instant specification. There are no compounds made with other hydrocarbons for R1 and also at the 6 position substitution.

The availability of the starting material that is needed to prepare the invention as claimed is at issue here.. As per MPEP 2164.01 (b):

A key issue that can arise when determining whether the specification is enabling is whether the starting materials or apparatus necessary to make the invention are available. In the biotechnical area, this is often true when the product or process requires a particular strain of microorganism and when the microorganism is available only after extensive screening. The Court in *In re Ghiron*, 442 F.2d 985, 991,169 USPQ 723, 727 (CCPA 1971), made clear that if the practice of a method requires a particular apparatus, the application must provide a sufficient disclosure of the apparatus if the apparatus is not readily available. The same can be said if certain chemicals are required to make a compound or practice a chemical process. *In re Howarth*, 654 F.2d 103, 105, 210 USPQ 689, 691 (CCPA 1981).

There are no starting material provided with respect to the the various hydrocarbon and "substituted" groups other than H.

Regarding solvates:- The claims are drawn to solvates, yet example presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

Re prodrugs.

Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. f) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience and would not constitute a person of ordinary skill in the art.

**7) The existence of working examples:** The instant specification does not have any working examples with respect to the various substitutents as given above, nor for the prodrugs or solvates. There is not data provided either.

**8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure:** In view of all the above factors, guidance and state of the art , it would require an undue amount of experimentation to make the invention of the claims with various substitutents , or for using them to treat or prevent the diseases ie. Pharmaceutical compositions also..

Taking the above eight factors into consideration, it is not seen where the instant specification enables the ordinary artisan to make and/or use the instantly claimed invention.

"A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention , not for vague intimations of general ideas that may or may not be workable."

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

***Claim Rejections - 35 USC § 102***

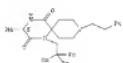
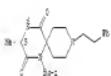
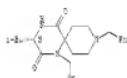
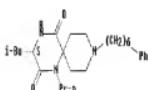
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/40227  
Himoru Habashita et al .

The reference discloses compounds of the formula



### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

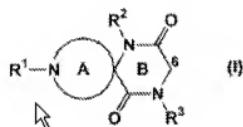
- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1625

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO

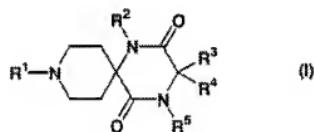
01/40227 Himoru Habashita et al.

Applicants claims are drawn to compounds of the formula



*Scope & Content of Prior Art MPEP 2141.01*

The prior art also discloses similar core.

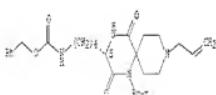


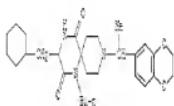
wherein R3 and R4 are

hydrocarbons and so is R1.

Some of the compounds disclosed are as given in the above rejection.

And some of them are as follows





*Difference between Prior Art and the claims MPEP 2141.02*

The difference between the prior art is that it does disclose some compounds that would read on the applicants and also some compounds with other functional groups.

*Prima Facie Obviousness , Rational and Motivation MPEP 2142-2413*

One of skill in the art would have been motivated to modify the compounds with substitution of other functional groups as those in the prior art to obtain the compounds of the invention.

The composition claims are also included as they have the same activity as those of the compounds of the invention and the preamble in the claims do not have any patentable weight.

***Conclusion***

Claims 1-13 are not found to be allowable.

Claims 14-16 are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Rita J. Desai/

Primary Examiner, Art Unit 1625

R.D.  
October 24, 2008